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Anxiety, depression and acupuncture: A review of the clinical research

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A B S T R A C T

Depression and anxiety together constitute a significant contribution to the global burden of disease. Acupuncture is widely used for treatment of anxiety and depression and use is increasing. The theoretical basis for acupuncture diagnosis and treatment derives from traditional Chinese medicine theory. An alternative approach is used in medical acupuncture which relies more heavily on contemporary neurophysiology and conventional diagnosis. Trials in depression, anxiety disorders and short-term acute anxiety have been conducted but acupuncture interventions employed in trials vary as do the controls against which these are compared. Many trials also suffer from small sample sizes. Consequently, it has not proved possible to accurately assess the effectiveness of acupuncture for these conditions or the relative effectiveness of different treatment regimens. The results of studies showing similar effects of needling at specific and non-specific points have further complicated the interpretation of results. In addition to measuring clinical response, several clinical studies have assessed changes in levels of neurotransmitters and other biological response modifiers in an attempt to elucidate the specific biological actions of acupuncture. The findings offer some preliminary data requiring further investigation.

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1. Depression and anxiety

Depression is projected to become the second leading contributor to the global burden of disease by 2020, affecting about 121 million people worldwide (WHO, 2006). It is described as 'a broad and heterogeneous diagnostic grouping, central to which is depressed mood or loss of pleasure in most activities' (NICE, 2004a,b). Two systems are available for the diagnosis of depressive disorders. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) uses an agreed list of ten depressive symptoms (WHO, 2007). 'Depressive episodes' are classified as mild, moderate or severe based on the number of symptoms present. Diagnoses defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) include single episode or recurrent major depressive disorder (APA, 2000). A major depressive disorder is defined as depressed mood or a loss of interest or pleasure in daily activities for at least 2 weeks.

Anxiety has been defined as a 'persistent feeling of dread, apprehension and impending disaster or tension and uneasiness' (Churchill et al., 2003). 'Anxiety disorders' is used as an umbrella term for a number of conditions including panic disorder, phobias, obsessive–compulsive disorder (OCD), generalised anxiety, traumatic stress disorder and anxiety disorder due to a general medical condition. The World Health Organisation estimated in 2004 that 1% of all disability adjusted life years lost in the world is due to post-traumatic stress disorder, obsessive–compulsive disorder and panic disorder combined (WHO, 2004).

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The most prevalent condition according to the Office for National Statistics (2000) is mixed anxiety and depression. Conventional treatment of these conditions is similar, usually involving tricyclic antidepressants, selective serotonin reuptake inhibitors and cognitive behavioural therapy (NICE, 2004a,b). However, the first two have been associated with adverse effects and poor compliance while the last is not widely available. Consequently, other treatments options are sought by patients. A national survey in the UK revealed that anxiety, depression and stress were among the most common reasons for seeking care from acupuncture practitioners with 11% of patients reporting a problem of this nature (MacPherson et al., 2006). Similar findings were reported in the USA (Simon et al., 2004).

The aetiologies of depression and anxiety are still not fully understood. A number of theories on the biological basis of depression have been proposed (Krishnan and Nestler, 2008). The earliest of these theories relates to low levels of noradrenaline and serotonin in the synaptic clefts (Bunney and Davis, 1965). These two neurotransmitters remain the focus of much of the work subsequently carried out but other neurotransmitters may also have a role (Barros et al., 2002). Recent studies have investigated the potential role of various neuropeptides (Madaan and Wilson, 2009), the immune system (Miller, 2010) and genetic factors (Smoller et al., 2009).

2. Acupuncture theory and practice

Acupuncture involves the stimulation of specific points on the body using a variety of techniques. It has been used for many years in China, Japan and Korea and forms part of what is now known as

traditional Chinese (or Oriental) medicine (TCM). Traditional acupuncture practice is based on the concept of a vital force or energy called 'Qi', flowing around the body along pathways known as 'meridians' (Wang et al., 2008). Stimulation of acupuncture points located along meridians is considered to balance the opposing forces (*yin* and *yang*) ensuring energy flow and thus maintenance or restoration of health. Diagnosis relies on the assessment of a complex matrix of signs and symptoms that are used to formulate individualised treatment regimens. The conventional diagnoses of depression and anxiety do not fit neatly into this system. In general, low moods and feeling anxious are considered to reflect a disruption in the flow of Qi, correction of which depends on a range of factors. Thus, patients with a conventional diagnosis of depression may be diagnosed with different TCM syndromes leading to differing treatment. Treatment sessions may include other interventions such as herbal mixtures. Related techniques including auricular acupuncture (acupuncture points on the ear), laser acupuncture (stimulation of acupuncture points with low level laser therapy) and acupressure (pressure applied at acupuncture points) may also be used.

In contrast 'Western medical' or 'medical' acupuncture practice is primarily based on contemporary neurophysiology and anatomy. Acupuncture points are thought to correlate to sites where external stimuli result in a greater sensory stimulus, for example, motor points of muscles and peripheral nerve bundles. Diagnosis is carried out conventionally and most medical acupuncturists use a combination of trigger points, tender points and segmental points for painful conditions (Filshie and Cummings, 1999). For non-painful, generalised conditions a selection of well-known traditional points may be used. Nevertheless, there is considerable variation in the styles of practice adopted by individual acupuncturists.

3. Clinical trials of acupuncture in depression

Clinical trials of acupuncture for depression first appeared in the medical literature in the mid 1980s. By the end of the 1990s, a sufficient number of studies had been published to justify a closer analysis. In 2002, a review of clinical studies concluded that acupuncture appeared promising as a treatment for depression (Jorm et al., 2002).

Subsequently, Smith and Hay (2004) evaluated seven randomised controlled trials with a total of 517 participants. Participants in the trials generally suffered mild to moderate depression. Electroacupuncture was used in four trials, manual acupuncture in two trials and a combination of electroacupuncture plus manual acupuncture in the remaining trial. The number of points stimulated varied: two points were used in several of the electroacupuncture trials, a larger number in those of manual acupuncture. Five trials compared acupuncture with medication; one compared acupuncture treatment with a wait list control group and in one trial acupuncture was assessed against sham acupuncture. A wide variation in the mode of stimulation, duration of needling, number of points used, depth of needling and needle stimulation and duration of the trials was highlighted. The Hamilton Rating Scale for Depression (HAM-D), which measures the severity of symptoms, was used as the primary outcome measure in six trials. Meta-analysis did not conclusively prove that medication was better than acupuncture in reducing the severity of depression or in improving depression, defined as remission versus no remission. Small sample sizes and poor quality of the trials led to the overall conclusion that there was insufficient evidence to determine the efficacy of acupuncture compared to medication, wait list control or sham acupuncture.

Mukaino et al. (2005) also evaluated the results of seven trials. Different inclusion criteria resulted in a slightly different set of trials being analysed although the total patient numbers were similar (509). The evidence was not conclusive on the effects of manual acupuncture versus sham or on whether acupuncture has an additive effect when given as an adjunct to antidepressants. The results suggested that the effect of electroacupuncture may not be significantly different from that of antidepressants, a finding supported by an analysis of studies from a Chinese database (Sha, 2005). The studies located were small and judged to be poorly designed, precluding firm conclusions, a finding replicated in a further review (Leo and Ligot, 2007). Variation in diagnostic methods (individualised Chinese diagnosis versus Western standardised diagnostic criteria) and treatment approaches (e.g. manual acupuncture at a range of acupoints, and electroacupuncture in two predetermined acupoints) in clinical trials continued to prove a problem (Halbreich, 2008).

Nevertheless, clinical trials continue to be published and in 2008, Wang et al. conducted a further meta-analysis. Only trials testing active acupuncture against 'sham' acupuncture were included: a total of eight trials involving 477 subjects. Sham techniques included stimulation of 'non-specific' points and superficial needling. Again, the quality of studies was reported as low. A significant difference was reported in the reduction of depression severity but the difference was small in clinical terms (mean difference in depression scores based on the HAM-D −0.65 95% CI −1.18 to −0.11). No difference was found in response rate defined as a 50% reduction in scores or in remission rate.

The majority of trials published since 2004 have been conducted in China and compare acupuncture against antidepressants. A total of 20 trials involving 1998 patients with major depressive disorder were identified and judged to be high quality (Zhang et al., 2009). The number of subjects studied ranged from 40 to 440 but most were relatively small with less than 100 participants. Treatment duration varied from four to 12 weeks, the majority being 4 to 6 weeks in duration and the number of acupuncture sessions ranged from 12 to 40. Manual acupuncture was used in 10 trials and electroacupuncture in the remaining 10 trials. The acupuncture points stimulated included those on the body, scalp and ear. The four most frequently used acupoints were Baihui (GV-20, vertex of the head), Yintang (EX-HN3, midway between the eyebrows), Taichong (LR-3, dorsum of foot between first and second metatarsals), and Shenmen (HT-7, transverse wrist crease). Little information is available on the rationale for the choice of points.

The analysis by Zhang et al. found acupuncture to be equivalent to antidepressants in reducing the symptoms of major depressive disorder and in effecting a clinical response. Acupuncture also appeared to offer advantages in terms of a lower incidence of adverse effects. There was insufficient evidence on whether combining acupuncture with antidepressants offered an advantage over antidepressants as sole therapy. However, no difference was found between acupuncture and sham acupuncture. This finding is reflected in the results of a trial conducted in the USA (Allen et al., 2006). The trial involved patients meeting DSM-IV criteria for depression, used HAM-D scores as the primary outcome measure and was well-designed. Acupuncture based on traditional Chinese medicine principles was compared with needling at non-specific points and with a wait list control group. Patients were treated twice weekly for the first 4 weeks then weekly for the next 4 weeks. Response rates after 8 weeks were relatively low and only reached 50% after 16 weeks. Both groups receiving acupuncture improved more than those on the waiting list but there was no evidence of a significant difference in efficacy between needling at specific and non-specific points. Similar findings have recently been reported in a large study of acupuncture in another chronic condition, low back pain (Cherkin et al., 2009). The reasons for this remain unclear; it may be that stimulation at non-specific points produces an effect, that effects are due to non-specific aspects of the intervention or that true differences have not been detected.

The most recent analysis of the evidence on acupuncture in depression is that provided by the updated Cochrane review published in 2010 (Smith et al., 2010). A total of 30 trials of

acupuncture were located including trials in post-stroke depression. The authors concluded that there was still insufficient evidence to recommend the use of acupuncture for depression, primarily because of the high risk of bias in the majority of trials.

A summary of trials published since 2007 is presented in Table 1. Studies were identified using recent systematic reviews, the Cochrane Central Register of Controlled Trials and by searching major databases using the terms 'acupuncture' and 'depression or depressive disorders'.

4. Clinical trials of acupuncture in anxiety

Comprehensive database searches conducted in 2004 succeeding in identifying 10 randomised and two non-randomised controlled trials of acupuncture in anxiety or anxiety disorders (Pilkington et al., 2007). Studies reporting on the effects on anxiety levels in patients with chronic medical or physical conditions were excluded but relevant trials in languages other than English were included and translated. Four randomised trials assessed the effects of acupuncture in generalised anxiety disorder or anxiety neurosis. Six focused on

acute anxiety in the perioperative period including pre-operative anxiety. No studies were located on acupuncture in specific anxiety disorders, for example panic disorder, phobias or obsessive–compulsive disorder.

Interpretation of the results of trials in generalised anxiety disorder or anxiety neurosis was difficult. This was due to similar problems to those encountered in trials in depression. Acupuncture treatment also varied between trials. For example, individualised acupuncture was used in one trial while acupuncture at five specific points was used in another. Control interventions included treatments such as behavioural desensitisation, sham acupuncture using non-specific points, biofeedback and drug therapy. In several cases the reported cure rates appeared unrealistically high. When acupuncture was compared with drug therapy, no difference in effects was found. This could be due either to the treatments being equally effective or to the trials being insufficiently powered for a valid assessment of equivalence. The single trial comparing acupuncture with sham acupuncture included only a small number of the participants diagnosed with an anxiety disorder, the majority suffering from mild depression.

Table 1
Trials of acupuncture in depression published since 2007.

Authors	Diagnostic criteria	N	Acupuncture Tx	Points used	Total sessions	Duration	Control Tx	Control Tx	Primary outcome measure	Result
Duan et al. (2009a)	ICD 10	95	EA + FLU	Baihui (GV 20), Yintang (EX-HN 3), frequency 120-250/min; plus body points based on symptoms	36	6 wks	FLU		HAM-D	NS; more rapid effect with EA; S for ADR
Duan et al. (2008)	CCMD-3	75	EA + FLU	Baihui (GV 20), Yintang (EX-HN 3), frequency 120-250/min; plus points based on symptoms	36	6 wks	FLU	EA	HAM-D	S (EA + FLU vs EA or FLU)
Fu et al. (2008)**	CCMD-2	440	MA	Taichong (LR 3), Hegu (LI 4), Baihui (GV 20), Yintang (EX-HN 3) plus 2 ear acupoints (Liver, Heart)	24	12 wks	FLU	NAN	HAM-D	NS (MA vs FLU); S (MA vs NAN); S for ADR (MA vs FLU)
Li and Liu (2007)	CCMD-3	56	EA + MA	Fengchi (GB 20), Anmian, Sishencong (EX-HN), Yintang (EX-HN 3), Baihui (GV 20), Shenmen (HT 7), Jianshi (PC 5), Hegu (LI 4), Taichong (LR 3), Sanyinjiao (SP 6), Qiuxu (GB 40), Shuaigu (GB 8), Zusanli (ST 36) plus points based on symptoms	42	6 wks	FLU or PAR		HAM-D	NS
Liu et al. (2009)	CCMD-3	41	EA + FLU	Baihui (GV 20) and Shenting (GV 24) or Yintang (EX-HN3), low frequency, plus points based on symptoms	42	6 wks	FLU		TESS	S
Qiao and Cheng (2007)*	CCMD	40	MA	Baihui (GV 20), Shenmen (HT 7)	40	8 wks	FLU		HAM-D	NS
Song et al. (2007)	DSM-IV	90	EA	Yintang (EX-HN3), Baihui (GV 20)	30	6 wks	FLU	Sham EA	HAM-D	NS
Xie and Li (2009)	ICD 10	120	MA	Zhongwan (CV 12) and Si-guan points [Taichong (LR 3) and Hegu (LI 4)] plus other points including Baihui (GV 20), Sishencong (EX-HN)		8 wks	FLU		HAM-D	NS; S for ADR
Whiting et al. (2008)	CISR	19	MA	Hegu (LI4), Shenmen (HT7), Sanyinjiao (SP6), Taichong (LR3), Fenglong (ST40) plus other points based on symptoms	12		NSN		BDI	Decreased scores (S not stated)
Zhang and Zhao (2007)*	CCMD	100	MA	Body and scalp points	28	4 wks	AMI		HAM-D	NS
Zhang et al. (2010)	DSM-IV	80	MA + FLU 10 mg + placebo	Baihui (GV20), Sishencong (EX-HN1), Yintang (EX-HN3), Shuigou (GV26), Neiguan (PC6), Shenmen (HT7), Taichong (Liv3), Hegu (LI4)	30	6 wks	NSN + FLU 20–30 mg		HAM-D	NS; S for ADR
Zhang et al. (2007a)	CCMD-3	42	EA + PAR	Baihui (GV 20) and Yintang (EX-HN3) plus other points according to symptoms, frequency 2 Herz	36	6 wks	PAR		HAM-D	S; NS for ADR
Zhang et al. (2007b)*	CCMD-3	80	EA	Baihui (GV 20), Yintang (EX-HN3) plus body points, frequency 50 Herz	40	6 wks	PAR		HAM-D	S

AMI amitriptyline; BDI Beck Depression Inventory; CCMD Chinese Classification of Mental Disorders; CISR Clinical Interview Schedule Revised; DSM Diagnostic and Statistical Manual of Mental Disorders; EA electroacupuncture; FLU fluoxetine; HAM-D Hamilton Rating Scale for Depression; ICD International Statistical Classification of Diseases; MA manual acupuncture; NAN non-acupoint needling (0.5 cm from specified acupoints); NS non-significant difference; NSN non-specific needling (superficial needling at sites not used for treating depression); PAR paroxetine; S significant difference; Sham EA 1 cm from points, no electrical current; TCM traditional Chinese medicine; TESS Treatment Emergent Symptom Scale; Tx treatment; * data adapted from Zhang et al., 2009; ** also reported as Fu et al., 2009.
Note: studies of post-stroke, comorbid, perinatal and menopausal depression and those in which acupuncture was part of a complex TCM intervention have not been included.

The quality of reporting of the studies of perioperative anxiety was generally better and the results indicated that acupuncture, specifically auricular acupuncture at defined acupuncture points, was more effective than acupuncture at a sham point. This conclusion was based on changes in scores on anxiety rating scales. Physiological changes, including changes in blood pressure and heart rate, were measured in several studies. These did not necessarily correlate with changes in anxiety scores which were based on symptom scoring systems or subjective assessment.

Further studies have been conducted subsequently on specific anxiety disorders. Three trials have focused on generalised anxiety disorder (Wang et al., 2006; Luo et al., 2007; Yuan et al., 2007). All three compared acupuncture with drug treatment over relatively short periods of time (4–6 weeks). Similar effects of acupuncture and drug therapy were reported but, as with previous trials, it is not clear whether these were designed to test equivalence and sample sizes were small. Trials in obsessive–compulsive disorder and post-traumatic stress disorder have also been published. To date the trials are too small in number and varied in design to provide a clear assessment of the potential effectiveness in specific anxiety disorders.

5. Measurement of biological effects in clinical trials

As described, the majority of trials of acupuncture in anxiety and depression use symptom scoring systems, rating scales or clinical assessment in measuring its effects. However, several trials have incorporated other measures alongside these. Measurement of changes in levels of neurotransmitters has been carried out as reported in a small randomised controlled trial of acupuncture in menopause-related depression (Zhou and Wu, 2007). Patients were treated with either acupuncture or fluoxetine and dopamine blood levels were found to increase to a greater extent in the acupuncture group. Noradrenaline and 5-hydroxy-indoleacetic acid increased in both groups and no significant difference was found between the groups. Plasma levels of neuropeptide Y have also been measured in a small preliminary study in patients suffering major depression. Levels were found to decrease during treatment with electroacupuncture (Pohl and Nordin, 2002).

Abnormality in G protein-coupled receptors (including serotonin, noradrenaline and acetylcholine receptors) in brain and peripheral blood cells has been closely related to the aetiology of disorders such as depression and to the action of antidepressants (Song et al., 2007). Consequently, the effects of treatment on the density of GTP-binding-proteins in platelet membranes have been investigated in a randomised controlled trial of 90 patients diagnosed with major depressive disorder. Thirty age and sex-matched non-depressed individual acted as controls. Antibodies were used to quantify the levels before and after treatment for 6 weeks with an antidepressant drug, electroacupuncture and sham electroacupuncture. A similar therapeutic effect was seen with all treatments. However, levels of Galphai and Galphaq were significantly higher in depression patients than in controls and were not reduced by treatments.

A similarly designed controlled trial investigated the effects of electroacupuncture on inflammatory response and T-helper 1 and 2 functions (Song et al., 2009). Previous research had suggested that an increase in inflammatory response and an imbalance between T-helper (Th) 1 and 2 functions have a role in the development of major depression. Ninety-five patients with major depressive disorder were treated for 6 weeks with electroacupuncture, fluoxetine or placebo with 30 volunteers acting as controls. Serum cytokine levels were measured by ELISA. An imbalance between the pro- and anti-inflammatory cytokines (IL-1 and IL-10), and between Th1 and Th2 cytokines (INF-gamma or TNF-alpha and IL-4) was recorded in untreated depressed patients. Electroacupuncture and fluoxetine treatment reduced the levels of pro-inflammatory cytokine IL-1beta thus having an anti-inflammatory effect. The balance between Th1

and Th2 systems was also restored by electroacupuncture. Studies in generalised anxiety disorder have taken a similar approach. For example, changes in levels of corticosteroid, adrenocorticotrophic hormone (ACTH) and platelet serotonin levels were measured in a trial in 86 patients with generalised anxiety disorder (Yuan et al., 2007). Patients were assigned to drug therapy, needling or a combination of both treatments. Statistically significant reductions in plasma level of ACTH and platelet content of serotonin after treatment were reported in all three groups, but no significant change was found in corticosteroid level. Magnetic resonance imaging has also been used recently to investigate and compare changes in the brain caused by electroacupuncture and fluoxetine (Duan et al., 2009b). Nevertheless, studies such as these are few in number and preliminary in nature.

6. Conclusions

Acupuncture is widely used to treat psychological problems such as anxiety and depression. The overall safety of acupuncture has been evaluated in several large scale studies which demonstrated that serious adverse events are rare (Witt et al., 2009; Melchart et al., 2004; White, 2004). Use of acupuncture in general is increasing (Barnes et al., 2007). Nevertheless, in the case of anxiety and depression many questions remain unanswered. A series of clinical trials have been reported for both anxiety and depression but because of the heterogeneity of these studies in terms of the acupuncture interventions and controls used, comparative effects cannot be effectively assessed. The rationale for treatment is also rarely reported and in many cases appears to be based on traditional acupuncture theory and concepts. Effects are measured using subjective measures such as symptom rating scales or clinical assessment.

Results of trials in acute short-term anxiety situations appear promising but the relevance to chronic conditions such as generalised anxiety disorder is also unclear. Studies assessing whether acupuncture is efficacious as an adjunct to other established treatment approaches may also be valuable. The challenges in designing adequate trials of acupuncture in depression have been explored by a team from the UK. To date investigations have focused on the methodological challenges (MacPherson et al., 2004; Schroer and MacPherson, 2009) and the feasibility of developing a standardised treatment protocol for depression (MacPherson and Schroer, 2007). The effects of acupuncture, specifically electroacupuncture, on a range of biological response modifiers have been the focus of preliminary studies. The limited research on this aspect possibly reflects the fact that the aetiology of depressive and anxiety disorders has not yet been fully explained.

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